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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/237,291	01/25/1999	JUDY CAROL YOUNG	SYS-2068	9391

1095 7590 12/31/2002

THOMAS HOXIE  
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ONE HEALTH PLAZA 430/2  
EAST HANOVER, NJ 07936-1080

EXAMINER

SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 12/31/2002

24

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/237,291

Applicant(s)

YOUNG ET AL.

Examiner

Mary M. Schmidt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 18 October 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 18-20,23-27,31-35,37-44,46 and 47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 18-20,23-27,31-35,37-44,46 and 47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 January 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/1/02 has been entered.

#### ***Claim Rejections - 35 USC § 103***

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 18-20, 23-27, 31-35, 37-44 and 46-51 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (US Patent 5,665,557), Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387) or Davis et al. (US Patent 5,599,703), in view of Ku et al, Kobayashi et al, Ramsfjell et al (IDS Reference AK), Ohmizono et al, Szilvassy et al, Escary et al., or Bodine et al, and further in view of Tushinski et al (IDS Reference AN), Fletcher et al., Bello-Fernandez et al, Hatzfeld et al., and Hanenberg et al. (Nature Medicine Vol. 2, No. 8) or Henenberg et al. (IDS Reference AR) for the same reasons of record as set forth in the Official Action on the Merits mailed 04/10/00, 01/04/01 and 08/13/01.

Applicant's arguments filed 10/1/02 and 10/18/02 have been fully considered but they are not persuasive.

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Claim 37 has been amended to specify that the method is a method of transducing human (instead of mammalian) CD34+ hematopoietic cells. The amendments to claims 24, 26, 27, 39, 40 and 41 specify that the claimed concentration ranges are "about" the specified concentration levels. The amendments to the claims have not changed the nature of the rejection since the Office action dated 4/10/00 taught on page 3 that the Murray et al. (U.S. Patent 5,665,557), Nakahata (U.S. Patent 5,861,315), Hoffman et al. (U.S. Patent 5,744,361), Fei et al. (U.S. Patent 5,635,387) and Davis et al. (U.S. Patent 5,599,703) all taught methods of isolating and culturing populations of human hematopoietic stem cells. Furthermore, this Office action taught the ranges of mpl, TPO, FL, IL-6, IL-3, LIF and/or c-kit used in '557, '315, '361, '387, and '703 as within the claimed ranges.

In the response filed on 10/18/02, page 3, applicant states that "[i]n a technical field that has proven to be highly unpredictable, Applicants are the first to demonstrate the advantages of including a combination of mpl ligand and flt3 ligand with or without additional cytokines in the culture system for HSC targeted for genetic manipulation and clinical protocols aimed at long-term engraftment."

However, Ku et al. also taught the combined use of mpl ligand and flt3 ligand on page 4124 as follows: first they taught that the Mpl ligand is the "physiological regulator of thrombopoiesis and is identical to thrombopoietin (TPO)."; then they taught that "we have observed that TPO can support formation of multilineage colonies from marrow cells of 5-fluorouracil (5-FU)--treated mice in synergy with Steel factor (SF, Kit ligand) or interleukin-3

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(IL-3). This observation is in agreement with the of Alexander et al. that Mpl knockout mice have reduced number of multipotential progenitors relative to wild-type mice.”; next they taught that experiments using soluble TPO receptor (sTPOR) on multilineage colony formation supported by the combination of TPO and SF does not suppress colony formation from primitive progenitors, and more pertinent to the instant claims, that “sTPOR, in synergy with SF or Flt3/Flk2 ligand (FL), can directly stimulate colony formation from primitive progenitors” and that “these observations may be important for *in vitro* manipulation of hematopoietic stem cells.” Thus, they do specifically teach the combination of mpl/TPO and flt3 ligand for use in stimulation of hematopoietic stem cell growth, as well as in combination with other cytokines. Kobayshi et al. further taught use of the combination of FL and TPO (see abstract) on growth of CD34+ cells. Furthermore, Ohmizono et al. taught in the abstract that “[w]e studied the effects of stem cell factor (SCF) and flt3 ligand (FL) on the *ex vivo* expansion of human umbilical cord blood (CB)-derived CD34+ cells in combination with various cytokines, including interleukin (IL-3, IL-6, IL-11), and c-Mpl ligand (thrombopoietin, TPO), in a short-term serum free liquid suspension culture system.” They thus also taught the use of the combination of flt3 and mpl. Ramsfjell et al. (abstract) further taught that “we also demonstrate that the majority of TPO-recruited CD34+CD38- progenitor cells have a multilineage differentiation potential, and that TPO promotes prolonged expansion of multipotent progenitors. Specifically, whereas progenitor cells were reduced in cultures containing only KL+FL, addition of TPO resulted in 40-fold expansion of multipotent progenitors following a 14-day incubation.”

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In view of the explicit teaching of these references to use the combination of mpl (TPO) and flt3 (FL) ligands in the growth of CD34+ hematopoietic cells, the prior art did in fact teach the standard quoted by applicant on page 5 of the response: “”some objective teaching in the prior art” or, alternatively, that there is “knowledge generally available to one of ordinary skill in the art [that] would lead that individual to combine the relevant teachings of the references.” In the instant case, the relevant teachings of the cited references are the use of the specific combination of the mpl(TPO) and flt3(FL) ligands with other cytokines in different art recognized concentrations for growth and use of hemopoietic stem cells.

Applicants state on page 6 of the response filed 10/18/02 that “[a]pplicants respectfully disagree with the Examiner and maintain that the Examiner has not met the burden of establishing a *prima facie* case of obviousness as the requisite showing of a motivation to combine these 18 references has not been demonstrated for reasons already made of record and further in view of the following remarks. Applicants take this opportunity to remind the Examiner that the pending claims are directed to methods for genetically modifying human hematopoietic stem cells (HSC) or human CD34+ hematopoietic cells comprising a subpopulation of HSC.”

The motivation to combine the cited references begins with the motivation provided by each reference cited to improve the growth conditions of hematopoietic stem cells for various purposes and to use certain combinations of growth factors and cytokines in this effort. The motivation to improve growth conditions in general of CD34+ cells is provided throughout the

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cited references. For example, Szilvassy et al. teaches in the first line of the abstract that “[a]ttempts to maintain or expand primitive hematopoietic stem cells *in vitro* without the concomitant loss of their differentiative and proliferative potential *in vivo* have largely been unsuccessful.” They state on page 4619, col. 1, that “[t]he present study was designed to assess the capacity of different cloned BM stromal cell lines to support the most primitive murine stem cell lines with competitive long-term repopulating activity.... We show that CRU numbers decline sharply when cultured on monolayers of SyS-1, S17, or PA6 cells. However, the addition of leukemia inhibitory factor (LIF) to SyS-1, but not S17 or PA6 cocultures, facilitates a maintenance of input CRU numbers by induction of early-acting cytokines including IL-6 and Steel Factor (SLF).... These data show an important role of LIF in maintaining repopulating stem cells by indirectly promoting cytokine expression by BM stroma. Furthermore, the ability to reconstruct stromal microenvironments by expression of simple combinations of early-acting hematopoietic growth factors should facilitate analysis of the molecular interactions of HSC self-renewal and/or differentiation *in vitro*.” They concluded on page 4627 that “[t]hese results raise the important future possibility that HSCs may be sustained *in vitro* on relatively simple stroma that have been molecularly engineered to express the appropriate spectrum of cytokines and/or extracellular matrix components that promote self-renewal *in vivo*.... Although the molecular mechanisms of stem cell self-renewal are not currently defined, it is clear that this approach represents a powerful tool in the identification of novel factors involved in HSC development, and could have far reaching implications for *ex vivo* stem cell expansion, gene therapy, and

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therapeutic transplantation.” Fernandez et al. further taught the motivation to use flt3 ligand in combination with specific growth factors in transducing dendritic cells with a retroviral vector and taught in the abstract that “[a]ddition of flt3-ligand (FL) to the aforementioned growth factors significantly enhanced cell expansion (41.7+/- 11.5 fold vs. 22.5 +/- 4.7 fold without FL)....” They thus specifically provided the motivation to use FL to enhance cell expansion in the role of transducing cells generated from CD34+ cord blood (CB) progenitor cells under serum-free conditions. As pointed out above, the Ku et al., Kobayshi et al., Ohmizono et al. and Ramsfjell et al. all taught the requisite motivation for what applicants alleged in the response is their invention: the combination of flt3(FL) and mpl(TPO) to improve growth conditions of HSCs.

As argued previously, the claims are broadly drawn to methods of genetically modifying a population of human hematopoietic stem cells with a vector, where the cells are cultured in fibronectin and the presence of mpl ligand and flt3 ligand to obtain modified HSCs. The cited references all teach different combinations of modifying HSCs with different specific combinations of cytokines embraced by the claims. As argued previously the addition of fibronectin would have been obvious in view of the use taught by Hanenberg et al. (“Optimization of Fibronectin-Assisted Retroviral Gene Transfer into Human CD34+ Hemopoietic Cells”) for use of fibronectin specifically to optimize retroviral gene transfer into human CD34+ hemopoietic cells. Therefore, the motivation taught in the prior art to transfer viral vectors into CD34+ hematopoietic cells was taught, the motivation to transfer under specific



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growth conditions of the cells was taught, as well as the motivation to use the specific growth conditions instantly claimed. While the references do not specifically mention each other in the body of the reference, they do all teach the benefits of certain HSC cell growth conditions and the general motivation to improve such conditions by use of different specific combinations of cytokines and growth factors.

Applicant has taken the position that references are divided into six groups although there is no teaching of these groups in previous Office actions. Applicant first argues that the Tushinski et al. reference and the Fletcher et al. references do not provide a teaching of the an mpl ligand in combination with a flt3 ligand. However, as stated in more detail above, the Ku et al., Kobayshi et al., Ohmizono et al. and Ramsfjell et al. were relied upon to have taught the requisite motivation for the combination of flt3(FL) and mpl(TPO) to improve growth conditions of HSCs. The Tushinski et al. reference was relied upon to have taught the use of IL-3, IL-6, SCF, LIF and flt3 in transduction of HSCs. Applicant further argues that Fletcher provides no motivation to combine their teachings with the other cited references. However, Fletcher et al. teaches on page 837 that “[a] major limiting factor in the development of retroviral vector-mediated gene transfer for treatment of diseases affecting the blood and blood-forming tissues has been the low infection efficiency of hemopoietic stem cells *in vitro*.... Although a 100% stem cell infection efficiency is not required to proceed from murine models to large animal models of gene therapy, the infection efficiency must be high enough such that all transplanted recipients exhibit hematopoietic repopulation with the differentiated progeny of at least one

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infected stem cell.... The large number of cells required for successful hematopoietic engraftment... could preclude selection techniques as a substitute for efficient stem cell infection.” On page 838 they continue with the statement that “[a] prediction of either of these models is that the provision of appropriate cytokines to bone marrow culture should enhance vector-mediated gene transfer to stem cells by stimulating self-replication, or by otherwise maintaining the stem cell proliferative and differentiative capacity.... We have been studying other recombinant cytokines... to determine whether they might improve stem cell survival and retroviral vector infection *in vitro*.” They thus provide ample motivation to provide cytokines which preserve and improve growth of stem cells in culture to maintain a proliferative and differentiative capacity for the use in transduction with a viral vector. As pointed out above, Ku et al., Kobayshi et al., Ohmizono et al. and Ramsfjell et al. further taught the requisite motivation for the combination of flt3(FL) and mpl(TPO) to improve growth conditions of HSCs.

Applicant further argues that the Bello-Fernandez et al. reference did not teach transformation of multi-lineage pluripotent HSCs, but instead taught use of dendritic cells. However, since the claims remain broadly drawn to methods of modifying any human hematopoietic stem cells, the claims continue to embrace the cells taught by Fernandez et al. which originate as HSCs. Applicant further argues that Fernandez et al. and Hatzfeld et al. do not do not provide a teaching of the an mpl ligand in combination with a flt3 ligand. However, as stated in more detail above, the Ku et al., Kobayshi et al., Ohmizono et al. and Ramsfjell et al.

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were relied upon to have taught the requisite motivation for the combination of *flt3*(FL) and *mpl*(TPO) to improve growth conditions of HSCs.

Applicant further argues that Hanenberg et al. and Hanenberg et al. do not provide a teaching of the an *mpl* ligand in combination with a *flt3* ligand. However, as stated in more detail above, the Ku et al., Kobayshi et al., Ohmizono et al. and Ramsfjell et al. were relied upon to have taught the requisite motivation for the combination of *flt3*(FL) and *mpl*(TPO) to improve growth conditions of HSCs. Applicant further states (page 11 of the response filed 10/18/02) that in these references “gene transfer efficiency was monitored 12-16 days following exposure of the CD34+ hematopoietic cells to retroviral infection, and long-term engraftment capabilities of the transduced cells was not assessed. One of skill in the art would recognize the while these references suggest the advantages of fibronectin for enhancing transduction efficiency of cultured hematopoietic stem cells *in vitro*, they are a mere invitation to experiment further, as use of this protocol for *ex vivo* genetic manipulation of quiescent human hematopoietic stem cells would not necessarily yield a transduced population of HSC capable of supporting long-term engraftment.” However, nowhere in the claims is the functional limitation found that the cells are cultured *ex vivo* or that the cells are used for long-term engraftment. Applicant is thus arguing limitations not found in the claims. Therefore, there is not “mere invitation” to practice further research, nor an obvious-to-try standard.

Applicant further argues individually the Murray et al. (U.S. Patent 5,665,557), Nakahata (U.S. Patent 5,861,315), Hoffman et al. (U.S. Patent 5,744,361), Fei et al. (U.S. Patent

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5,635,387) and Davis et al. (U.S. Patent 5,599,703) references. As noted previously, these references do not teach all the claimed limitations, and are relied upon primarily to teach the use of different combinations of cytokines (mpl, TPO, FL, IL-6, IL-3, LIF and/or c-kit) and different concentrations for the optimized growth of HSCs. For instance for the Davis et al. reference, applicant states on page 18 of the response filed 10/18/02 that “one of skill in the art would not have been motivated to look to the other cited references for guidance as to additional elements to combine with the culture medium disclosed and/or claimed in the Davis et al. reference, as the culture medium taught in this patent is suitable for the intended objective, i.e., [i.e.,] culturing of human hematopoietic CD34+ stem cells and CD34+ progenitor cells to amplify/expand the number of these cells *in vitro*.” However, as reiterated above, Ramsfjell et al. taught 40-fold improved growth of pluripotent HSCs with the combination of mpl and flt3 ligands. Fernandez et al. also taught improved growth expansion of HSCs with FL ligand. As Szilvassey et al. taught, the growth expansion of HSCs allows for improved use of the cells *in vitro*, including transduction thereof. And Tsukamoto et al. (U.S. Patent 5,750,397) summarized why such results are significant by teaching that the “stem cell population constitutes only a small percentage of the total number of leukocytes in bone marrow.” (Col. 1) They state in col. 2 that “possession of the stem cell will allow for identification of growth factors associated with its self regeneration....” Thus the teachings of the other references indicating retaining multipotent lineages of HSCs with for instance the flt3 and mpl ligands, as well as using other cytokines, is a continual improvement toward the ultimate goal in the art to understand completely the role of

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each and every cytokine in the regeneration of stem cells so that they may be effectively grown in large quantities for the retention of multipotential activity.

As summarized by applicant on page 21 of the response filed 10/18/02, Bodine et al. taught the positive effects of IL-3, SCF and IL-6 on the repopulation of HSCs in culture. However, applicant maintains the argument that there is no motivation to combine these teachings with the other cited references to obtain the claimed invention. However, Ohmizono et al. clearly taught motivation to “develop a culture system which can expand mature and immature hematopoietic stem and progenitor cells *in vitro*.” Furthermore, Kobayashi et al. taught specifically the synergism achieved between SF,FL and TPO in the survival and proliferation of primitive human hematopoietic progenitors. Therefore, there was both motivation to generally and specifically practice the claimed methods, as well as an expectation of success to achieve some growth, repopulation, expansion of HSCs using the claimed cytokines, and further, in combination with the references supporting viral transduction of HSCs, to provide some transduction of such cells.

In regards to the Ku et al. reference, application argues on page 22 of the response filed 10/18/02 that “this reference fails to teach culture of human multi-lineage pluripotent stem cells in the presence of an mpl ligand and a ckit ligand, more particularly, in combination with fibronectin, to achieve Applicants’ claimed method of genetic modification of this type of hematopoietic cells.” However, again, applicant is arguing limitations not found in the claims. The claims as filed are broadly drawn to any type of hematopoietic stem cells. In the case of the

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Ohmizono et al reference, applicant argues that “[i]n all cases, the desired outcome is expansion of committed progenitors, and hence this reference does not report on the effects of the various cytokine cocktails on the ability of cultured CB-derived CD34+ hematopoietic stem cells to maintain their pluripotent state; the reference is not concerned with hematopoietic stem cell proliferation, rather, it is concerned with expansion of the stem cell population, and hence manipulation of these stem cells to commit to a particular hematopoietic cell lineage....”

However, as pointed out above, the claims are not limited to a particular type of HSCs, but rather embrace any type of HSC. Furthermore, Ohmizono et al. does provide at least the motivation for the development of primitive progenitor cells on page 524, in col. 2 despite the fact that they provide more experimental data regarding the expansion of the committed cells.

Similarly, in the case of the Kobayashi et al. reference, application argues on page 24 of the response filed 10/18/02 that “this reference fails to suggest that this combination of factors would be applicable to a protocol for genetic modification of human hematopoietic cells, more particularly multi-lineage pluripotent HSC.” However, again, applicant is arguing limitations not found explicitly in the claims. Similarly, in the case of the Ramsfjell et al. reference, applicant states that “it had not yet been demonstrated whether TPO or any other known cytokine might expand the true long-term reconstituting pluripotent stem cells.... True to this statement, Ramsfjell et al. provide no data with respect to long-term engraftment potential of their cultured HSC.” However, again, this limitation/teaching is not instantly claimed. The claims instead read on growth and transduction of any HSC.

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Applicant states that there is no motivation to combine either Kobayshi et al. or Ramsfjell et al. with any of the other cited references. However, since both of these references teach the recited use of TPO and FL ligands in the growth of HSCs, the Hanenberg et al. teaches enhanced retroviral delivery to HSCs with the use of fibronectin, one of ordinary skill in the art would have been motivated to use fibronectin for the benefits taught by Hanenberg et al. in the retroviral delivery to HSCs. Furthermore, other references such as Tushinski et al., Fletcher et al., Bello-Fernandez et al. And Hatzfeld et al. taught retroviral mediated transfer to HSCs in culture. The remaining references taught generally motivation to grow HSCs in culture and the use different combinations of cytokines such as those instantly claimed in the dependent claims, for the benefits taught in each of the recited references.

Applicant further argues on page 27 of the response filed 10/18/02 that “the prior art was in agreement as to the difficulty of gene transduction of the stem cell pool through to serve as the source of multi-lineage pluripotent HSC necessary for successful long-term engraftment, i.e., those stem cells capable of self-renewal as well as proliferation of multipotent progenitors.” However, as pointed out above, the claims as currently pending do not require that the HSCs are capable of self-renewal or that they are used in successful long-term engraftment. The instant claims as currently written embrace any type of HSC. Furthermore, all the cited references, establish some expectation of success to grow different types of HSCs in culture successfully with different combinations of cytokines, including those instantly claimed; further, to transduce

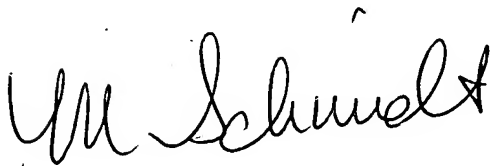
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capable of self-renewal or that they are used in successful long-term engraftment. The instant claims as currently written embrace any type of HSC. Furthermore, all the cited references, establish some expectation of success to grow different types of HSCs in culture successfully with different combinations of cytokines, including those instantly claimed; further, to transduce certain types of HSCs with vectors such as retroviral vectors; further, the improved benefits of the use of fibronectin in the transduction of such retroviral vectors in to HSCs.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

A handwritten signature in cursive script, appearing to read 'M. M. Schmidt', with a stylized flourish at the end.

M. M. Schmidt  
December 28, 2002